

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

APOTEX INC.,
Petitioner,

v.

CELGENE CORPORATION,
Patent Owner

Case IPR2023-00512
Patent 8,846,628

**PATENT OWNER'S PRELIMINARY RESPONSE
UNDER 37 C.F.R. § 42.107**

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PATENT OWNER'S EXHIBIT LIST

No.	Exhibit
2001	Declaration of Dr. Corey Berkland
2002	FDA approves Onureg [®] (azacitidine tablets) for acute myeloid leukemia ("FDA Approves Onureg [®] ")
2003	Aparicio 2002 ("Aparicio")
2004	Beisler 1977 ("Beisler")
2005	Reserved
2006	Canadian Product 200mg Onureg [®] Product Information
2007	Canadian Product 300mg Onureg [®] Product Information
2008	Canadian Product Monograph Onureg [®]
2009	Chabner 1973 ("Chabner")
2010	Chen 2008 ("Chen")
2011	Cheung 1984 ("Cheung")
2012	Čihák 1965 ("Čihák")
2013	European Commission Decision 17.6.21
2014	Connors 1986 ("Connors")
2015	Evans 1988 ("Evans")
2016	FASTtrack 2010 ("FASTtrack")
2017	Gaubert 2001 ("Gaubert")
2018	Kaminskas 2005 ("Kaminskas")

No.	Exhibit
2019	Kissinger 1986 (“Kissinger”)
2020	Lieberman 1990 (“Lieberman”)
2021	Lin 1981 (“Lin”)
2022	Mund 2006 (“Mund”)
2023	National Cancer Institute 1978 (“National Cancer Institute”)
2024	Notari 1975 (“Notari”)
2025	Onureg [®] Label
2026	International Pat. Appl. Pub. No. WO2009/139888 (“WO2009/139888”)
2027	Pitřhová 1965 (“Pitřhová”)
2028	Remington 2005
2029	Stresemann 2008 (“Stresemann”)
2030	U.S. Pat. Pub. No. US20040186065A1 (“Ionescu-065”)
2031	Weiss 1972 (“Weiss”)
2032	Celgene v. Accord 1:21-cv-01795-RGA Doc 40
2033	U.S. Pat. No. 7,189,740 (“Zeldis”)
2034	Glover 1987 (“Glover”)
2035	U.S. Pat. No. 6,887,855 (“Ionescu-855”)
2036	U.S. Pat. No. 7,078,518 (“Ionescu-518”)
2037	U.S. Pat. No. 7,772,199 (“Ionescu-199”)
2038	U.S. Pat. Pub. No. US20060247189 (“Ionescu-189”)

No.	Exhibit
2039	U.S. Pat. Pub. No. US20100298253 (“Ionescu-253”)
2040	Ward 2007 (“Ward”)
2041	International Pat. Appl. Pub. No. WO2008/028193 (“WO2008/028193”)
2042	Gibson Supplemental
2043	Lieberman Vol. 2
2044	International Pat. Appl. Pub. No. WO2004/082618 (“WO2004/082618”)
2045	Celgene v. Accord 1:21-cv-01795-RGA Doc 35
2046	Reserved
2047	Savage 1967 (“Savage”)

I. INTRODUCTION

U.S. Patent No. 8,846,628 (the “’628 patent”) claims pharmaceutical compositions and methods of use for the oral administration of 5-azacytidine, which is used for the treatment of certain types of leukemia. Scientists had known about 5-azacytidine and its anticancer properties for decades before the ’628 patent. However, the compound was known to be chemically unstable, particularly in the harsh acidic environment of the stomach, and to be enzymatically metabolized. As a result, prior to the invention of the ’628 patent, no one had successfully developed an oral formulation of 5-azacytidine. And to the extent that anyone tried to develop an oral formulation, those prior efforts focused on the use of “enterically coated” tablets to protect 5-azacytidine against degradation in the stomach.

The inventors of the ’628 patent made the surprising discovery that it is possible to treat cancer patients by orally administering 5-azacytidine tablets without an enteric coating. Their discovery is described and claimed in the ’628 patent and ultimately resulted in the development of the medicine Onureg[®], which is the first orally administered tablet of 5-azacytidine approved by the FDA.

The Board should deny institution against all challenged claims of the ’628 patent for two independent reasons.

First, the Petition fails to establish that the limitation of a “non-enteric coated tablet” in all challenged claims was disclosed or would have been obvious in view of the cited art. The Petition relies exclusively on the disclosure in Ionescu that tablets “may be coated with a concentrated solution of sugar” (Petitioner’s “sugar-coated tablets”) for this limitation. *See* Ex.1004-0015(Ionescu) 13:16-18; Pet., 22. But sugar-coated tablets are not synonymous with non-enteric coated tablets; indeed, Petitioner’s own cited art discloses sugar coatings on enterically coated tablets. And Petitioner fails to establish obviousness and a reasonable expectation of success in view of challenges known in the art (*e.g.*, the known chemical instability of 5-azacytidine in the acidic environment of the stomach).

Second, this Petition merits discretionary denial under 35 U.S.C. § 325(d). The Examiner considered the disclosure of Ionescu—Petitioner’s primary reference—at least five times; indeed, the same portions of the reference relied upon by the Petition were called out in an International Search Report considered during prosecution. And Petitioner has not identified error or anything about Ionescu that the Examiner allegedly misunderstood or overlooked. The expert declarations add no material evidence the Examiner missed in his analysis. Thus, denying institution would best serve the integrity of the patent system.

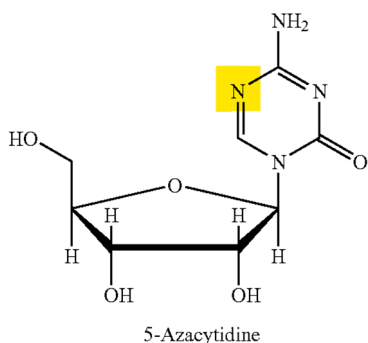
Petitioner cannot demonstrate that it is reasonably likely to prevail in establishing the unpatentability of any challenged claim, and the Board should decline to institute *inter partes* review.

II. BACKGROUND

A. State of The Art

1. 5-Azacytidine

5-azacytidine is a nucleoside similar to the naturally occurring nucleoside, cytidine. Ex.1001('628 patent), 2:37-62. 5-azacytidine possesses a nitrogen atom in place of a carbon atom present in cytidine, which is highlighted in the structure below:



Id., 2:48-62. Cancer cells incorporate 5-azacytidine into DNA and RNA. *Id.*, 3:9-27. Upon incorporation, 5-azacytidine “restor[es] normal functions” by promoting “re-expression of genes involved in normal cell cycle regulation, differentiation and death” leading to “the death of rapidly dividing cells, including cancer cells....” *Id.*, 3:9-22.

Researchers first synthesized 5-azacytidine in the early 1960s.

Ex.2012(Čihák); Ex.2027(Pitřhová); Ex.2001(Berkland Decl.) at ¶46. The first European and United States clinical trials with 5-azacytidine were underway in 1967 and 1970, respectively. Ex.2034(Glover), 737; Ex.2001(Berkland Decl.) at ¶46. Scientists had identified 5-azacytidine's anti-tumoral effect as early as 1972. Ex.2031(Weiss); Ex.2001(Berkland Decl.) at ¶46. For forty years, the field worked to develop pharmaceutically acceptable formulations, including oral formulations, of 5-azacytidine without success. It was not until May 2004 that the FDA approved *intravenous or subcutaneous* injection of 5-azacytidine, which was marketed as Vidaza®. Ex.1007(Vidaza® Label 2004); Ex.2018(Kaminskas); Ex.2001(Berkland Decl.) at ¶46.

2. Challenges to developing an oral formulation of 5-azacytidine

Prior to the December 5, 2008, the alleged priority date of the inventions described in the '628 patent,¹ a person of ordinary skill in the art ("POSA") would have expected that 5-azacytidine would have been degraded by the stomach, which has a very acidic pH that can reach values of about 1. Pet., 40; Ex.1002(Buckton Decl.), ¶138; Ex.1003(Batchelor Decl.), ¶41; Ex.2015(Evans), 1035; Ex.2043(Lieberman Vol. 2), 349-50; Ex.2001(Berkland Decl.) at ¶71; *see also id.* at ¶¶68-78. As Petitioner's experts concede, it was widely understood that 5-azacytidine was unstable and underwent rapid hydrolysis that would result in its break down in the stomach before a therapeutically effective amount of the drug could be absorbed in the gastrointestinal tract. Ex.1002-0065(Buckton Decl.), ¶119; Ex.1003-0020(Batchelor Decl.), ¶¶34-35; Ex.1014(Chan), 807; Ex.1021(Sands), ¶[0012]; Ex. 1034-0001(Stoltz); Ex.2014(Connors), 239;

¹ Petitioner contends that the earliest effective filing date of the challenged claims is December 5, 2008, which corresponds to the second of three provisional applications to which the '628 patent claims priority. Pet., 19. For the purposes of this POPR only, and without conceding the priority date, Patent Owner has applied the date of December 5, 2008 to the challenged claims.

Ex.2041(WO2008/028193), ¶¶[0024]-[0025]; Ex.2001(Berkland Decl.) at ¶¶64-78.

Thus, a POSA attempting to develop an oral tablet formulation of 5-azacytidine would have understood that any successful formulation would have to address this acid instability in the stomach to deliver a therapeutically effective amount of the drug to a patient. Ex.2001(Berkland Decl.) at ¶¶66-67. Significantly, in its challenges to the independent claims of the '628 patent, the Petition does not engage or explain how a POSA would have addressed hydrolytic degradation. Pet., 21-23, 31-38, 58-62.²

Additionally, a POSA attempting to develop an oral tablet formulation in December 2008 would have been concerned that a second pathway—enzymatic cytidine deamination—would also rapidly degrade 5-azacytidine.

Ex.2001(Berkland Decl.) at ¶¶66-67, 79-85; Ex.2043(Lieberman Vol. 2), 349

² Petitioner's expert, Dr. Batchelor, attempts to explain how to account for hydrolytic degradation only in the context of certain dependent claims. *See, e.g.*, Ex.1003(Batchelor Decl.), ¶¶34-36, 46-47; Pet., 30-31, 50-51. Patent Owner disagrees with Dr. Batchelor's method to account for this degradation, along with other issues in her analysis, but does not address these here because her analysis is limited to certain dependent claims only.

(disclosing that “[d]rugs are metabolized by enzyme systems of the body” and “[t]he net effect may be inactivation or detoxification of the compound....”). The prior art recognized that 5-azacytidine “suffers [] from several drawbacks” including “the ubiquitous cellular enzyme cytidine deaminase (CDA) since deamination of [5-azacytidine] results in total loss of activity.” Ex.2017(Gaubert), 837-838; Ex.2001(Berkland Decl.) at ¶81. This “degradation of [] cytidine analog[s]” such as 5-azacytidine “by cytidine deaminases” was associated with “[t]he poor bioavailability of such cytidine analogs....” Ex.1021(Sands), ¶[0012]; Ex.2001(Berkland Decl.) at ¶81.³ Again, a POSA would have understood that cytidine deaminases would also metabolize 5-azacytidine before a therapeutically effective amount of the drug could be absorbed in the gastrointestinal tract, thus complicating any oral formulation development. *See, e.g.*, Ex.1021(Sands), ¶¶[0012], [0029]-[0030]; Ex. 1034-0001(Stoltz); Ex.2001 (Berkland Decl.) at ¶¶65-67.

Further, a POSA would have understood that drug formulation development is a complicated process. Ex.2001(Berkland Decl.) at ¶64. For instance, “[c]ertain

³ Neither of Petitioner’s experts nor the Petition addresses the instability of 5-azacytidine due to enzymatic degradation.

pharmaceutical agents, particularly...many chemotherapeutic agents, can only be given parenterally because they are inactivated in the gastrointestinal tract when given by mouth.” Ex.2028(Remington 2005) at 802; Ex.2001(Berkland Decl.) at ¶64. Gibson, cited by Petitioner in Grounds 2 and 3, states that formulating any pharmaceutical dosage form involves finding “an equilibrium between the bioavailability of the product, its chemical and physical stability and the technical feasibility of producing it” because “[a]ny changes made to a formulation in an attempt to optimise one of these properties” was known to “likely [] have an effect on the other[s]” which “is *especially true of immediate-release solid dosage forms*.”⁴ Ex.1006-0032(Gibson); Ex.2001(Berkland Decl.) at ¶64. Thus, it would have been well understood by a POSA in December 2008 that developing therapeutic, oral tablet 5-azacytidine formulations to overcome the harsh acidic environment of the stomach and enzymatic metabolism was both necessary and challenging. Ex.2001(Berkland Decl.) at ¶66-67.

Due to these numerous challenges, it took many years to develop an oral tablet formulation of 5-azacytidine, even after the FDA approved *intravenous or subcutaneous* administered 5-azacytidine (Vidaza®). Ex.1007(Vidaza® Label

⁴ All quoted emphasis is added unless otherwise noted.

2004); Ex.2018(Kaminskas); Ex.1001('628 patent), 3:54-56; Ex.2025(Onureg[®] Label); Ex.2001(Berkland Decl.) at ¶¶46-47. The combination of chemical instability and enzymatic instability frustrated development of 5-azacytidine formulations for oral delivery. Ex.1001('628 patent), 3:54-56; Ex.2001(Berkland Decl.) at ¶47. Because “[a] drug administered as a tablet...must be released and reach its site of action in an active state before it can exert a pharmacological response,” a POSA would have recognized the above degradation pathways as impeding non-enteric coated oral formulations of 5-azacytidine. Ex.2043(Lieberman Vol. 2), 352-53; Ex.2001(Berkland Decl.) at ¶¶64-67.

3. A POSA would have attempted to develop enteric coated tablets

To overcome these challenges, a POSA would have attempted to protect 5-azacytidine from degradation by using an enteric coating. Ex.1001('628 patent), 3:58-65 (citing Ex.1021(Sands)); Ex.2001(Berkland Decl.) at ¶67. Enteric coated tablets are delayed release formulations that are not soluble in the highly acidic stomach but readily dissolve in the near neutral pHs of the intestines once the tablet has passed through the stomach. Ex.1006-0068(Gibson), -0070; Ex.1030-0049(Remington); Ex.2015(Evans), 1035; Ex.2043(Lieberman Vol. 2), 349-50; Ex.2001(Berkland Decl.) at ¶49. Enteric coated tablets are used in situations where release of compounds in the stomach results in undesirable effects including

compound degradation or inactivation by stomach contents. Ex.1006-0068(Gibson); Ex.1030-0049(Remington); Ex.2001(Berkland Decl.) at ¶49. In contrast to an enteric coated tablet, a non-enteric coated tablet does not contain a coating designed to prevent release of the drug in the acidic environment of the stomach. Ex.1001('628 patent), 11:42-45; Ex.2001(Berkland Decl.) at ¶49. Thus, it was well understood by a POSA in December 2008 that an enteric coated tablet, rather than a non-enteric coated tablet, should be used for an oral formulation to protect 5-azacytidine from degradation by the harsh, acidic stomach environment to the extent a POSA would have been motivated to make an oral tablet of 5-azacytidine at all. *See* VIII.B; Ex.2001(Berkland Decl.) at ¶¶57, 77, 83.

4. Onureg®

Contrary to the expectations taught in the art, the inventors developed a non-enteric coated tablet of oral 5-azacytidine as disclosed and claimed in the '628 patent. Ex.1001('628 patent), claims 1, 28. This non-enteric coated tablet formulation of oral 5-azacytidine was approved by the FDA in September 2020 as Onureg®, almost fifty years after scientists had identified 5-azacytidine's anti-tumoral effect and more than a decade and a half after FDA-approval of the injectable formulation Vidaza®. Ex.2002(FDA Approves Onureg®); Ex.1007(Vidaza® Label 2004); Ex.2018(Kaminskas); Ex.2025(Onureg® Label).

Onureg[®], which has been granted orphan drug designation, became the first oral tablet formulation of 5-azacytidine approved for continued treatment of patients with acute myeloid leukemia (“AML”) who achieved remission following intensive induction chemotherapy and are not able to complete intensive curative therapy. Ex.2025(Onureg[®] Label), 1. Canada and Europe followed suit, approving Onureg[®] in January and June 2021, respectively. Ex.2006(Canadian Product 200mg Onureg[®] Product Information); Ex.2007(Canadian Product 300mg Onureg[®] Product Information); Ex.2008(Canadian Product Monograph Onureg[®]); Ex.2013(European Commission Decision 17.6.21).

B. The '628 Patent

The inventions claimed in the '628 patent relate to a pharmaceutical composition comprising therapeutically effective amounts of 5-azacytidine for oral administration in a non-enteric coated tablet as well as methods for treating diseases and disorders (*e.g.*, AML or myelodysplastic syndromes (MDS)) using these compositions. Ex.1001('628 patent), Abstract, 6:56-65, 11:42-48, claims 1, 28; Ex.2001(Berkland Decl.) at ¶¶31-33.

As discussed above and explained in the '628 patent, it was known in the art as of December 2008 that “oral delivery of cytidine analogs has proven difficult due to combinations of chemical instability, enzymatic instability, and/or poor

permeability.” Ex.1001(’628 patent), 3:54-56. The ’628 patent explains that “[p]revious attempts to develop oral dosage forms of cytidine analogs have ***required enteric coating of the drug core*** to protect the active pharmaceutical ingredient (API) from what was understood and accepted to be ***therapeutically unacceptable hydrolysis in the stomach***, such that the drug is preferably absorbed in specific regions of the lower gastrointestinal tract....” *Id.* 3:58-65. The ’628 patent notes that a POSA also would have been concerned with hydrolysis during formulation, and coatings were thus limited to organic solvent-based systems. *Id.* 4:1-7.

Unexpectedly, the inventors found that “formulations comprising...5-azacytidine...and, optionally, one or more excipients...effect[ing] an immediate release of the API upon oral administration” were therapeutically effective. Ex.1001(’628 patent), 34:30-36; 4:21-27. The ’628 patent specification further describes non-limiting embodiments of methods of treating disorders, including AML, with non-enteric coated tablets comprising 5-azacytidine. *See, e.g., Id.*, 57:46-63, 68:47-73:8. These novel non-enteric coated formulations “demonstrated bioavailability in patients” with “positive clinical activity [for] patients” and with “[n]o safety issues....” *Id.*, 71:39-44. Additionally, they also “provided a superior

percent exposure...[compared to] enteric-coated azacitidine formulations”⁵ despite being released in the harsh environment of the stomach. *Id.*, 73:1-6.

III. PROSECUTION HISTORY OF THE '628 PATENT

U.S. Patent Application 12/466,213 (the “’213 application”) underwent extensive and substantive examination at the Patent Office before being properly granted as the ’628 patent.

Before examination, Applicant submitted a first IDS including three versions of Ionescu, the primary reference cited in the Petition. *See* Ex.1022-0185-0187(IDS submitted April 2, 2010, disclosing U.S. Pat. Nos. 6,887,855 (“Ionescu-855”) and 7,078,518 (“Ionescu-518”) and U.S. Pat. Pub. No. US2006/0247189 (“Ionescu-189”), which are substantively identical to Ionescu); Pet., 1-4.

Applicant’s first IDS also included an International Search Report (“ISR”) relating to an International Patent Application in the same family as the ’213 application. *See* Ex.1022-0187(IDS submitted April 2, 2010). The ISR submitted by Applicant cites to another reference substantively identical to Ionescu. Ex.1022-0187(IDS submitted April 2, 2010); Ex.1022-0633-0636(ISR citing U.S. Pat. Pub. No.

⁵ “5-azacytidine” and “azacitidine” are interchangeable terms for the same compound. *See* Ex.1001(’628 patent), 2:33-35.

US2004/0186065 (“Ionescu-065”)). The Examiner considered this IDS and the cited references before issuing a first Office Action rejecting the claims as both allegedly anticipated and obvious. Ex.1022-0707-0709(IDS considered July 19, 2011); *see also* Ex.1022-0646(Office Action dated August 1, 2011, disclosing “One Information Disclosure Statement (IDS) filed April 2, 2010, has been received with all cited references, annotated, and made of record”), -0651-0654.

Along with a response to the first Office Action, Applicant submitted a second IDS that included two additional references with disclosures that are substantively identical to Ionescu. Ex.1022-0735(IDS submitted December 1, 2011, disclosing U.S. Pat. No. 7,772,199 (“Ionescu-199”) and U.S. Pat. Pub. No. US2010/0298253 (“Ionescu-253”)). The Examiner considered both references and “carefully reviewed the prior art of record cited above” before issuing a second Office Action withdrawing the anticipation rejection. Ex.1022-1100(IDS considered February 23, 2012); *see also* Ex.1022-1074(Office Action dated Feb. 28, 2012, disclosing “One additional or supplemental Information Disclosure Statement (1 IDS) filed December 1, 2011, has been received with all cited non-US patent references, annotated, and made of record.”), -1082.

Shortly after the second Office Action issued, and before another communication from the Patent Office, Applicant submitted a third IDS disclosing

Ionescu (Ex.1022-1129(IDS submitted September 5, 2012 disclosing International Pat. Appl. No. WO2004/082619 (Ex.1004, “Ionescu”))), which the Examiner considered (Ex.1022-2027(IDS considered August 24, 2013); *see also* (Ex.1022-2017(Office Action dated August 29, 2013 disclosing an “additional or supplemental Information Disclosure Statement[]...filed September 5, 2012...ha[s] been received with all cited non-US patent references, annotated, and made of record.”)).

Following a third Office Action, Applicant filed a response, successfully arguing that “[a] novel and unique element of the claimed composition is the absence of an enteric coating, *i.e.*, a coating that is designed to release the active ingredient beyond the acidic environment of the stomach when orally administered.” Ex.1022-2072-2073(Office Action Response dated February 27, 2014). Applicant’s response was accompanied by a declaration of Dr. Charles L. Beach under 37 C.F.R. 1.132, which explained that “one of ordinary skill in the art at the time the ’213 application was filed would not have found it obvious to pursue an immediate-release composition of 5-azacytidine, *e.g.*, a non-enteric coated tablet, for oral administration.” Ex.1022-2086(Beach Decl.); Ex.1022-2078-2079(Office Action Response dated February 27, 2014). Dr. Beach explained that at the time of the application, 5-azacytidine was only approved for

intravenous or subcutaneous administration and that there was a strong prejudice in the art against developing an immediate release, non-enteric coated tablet formulation of 5-azacytidine. Ex.1022-2087-2089(Beach Decl.); Ex.1022-2073(Office Action Response dated February 27, 2014). Additionally, Dr. Beach pointed to support from post-filing data as well as data present in the '213 application itself demonstrating that the oral, non-enteric coated tablet formulations of 5-azacytidine recited in the then-pending claims exhibit unexpected pharmacokinetic, pharmacodynamic, and clinical properties. Ex.1022-2090-2092(Beach Decl.); Ex.1022-2079-2084(Office Action Response dated February 27, 2014).

The Examiner credited the “applicant’s response including [the] extensive and detailed declaration” of Dr. Beach in the Notice of Allowance. Ex.1022-2138(Notice of Allowance dated May 28, 2014). “[T]he rejections of record are inappropriate in view of the prior art cited, and that this conclusion is buttressed in several different ways by the detailed analysis of the instant cited prior art presented in [Dr. Beach’s] declaration.” Ex.1022-2138(Notice of Allowance dated

May 28, 2014).⁶ The Examiner also noted that the “surprisingly high anti-neoplastic medicinal activities of the claimed non-enteric coated pharmaceutical composition, has been identified as unexpected, and therefore...is also proper basis to argue in favor of a conclusion[] opposite to the previously asserted conclusions of obviousness.” Ex.1022-2138(Notice of Allowance dated May 28, 2014).

Further, the Examiner credited the “applicant’s amendments...to the claims together with applicant’s arguments made in parallel with the noted declaration” and allowed the claims that issued in the ’628 patent. Ex.1022-2138-2139(Notice of Allowance dated May 28, 2014).

IV. PERSON OF ORDINARY SKILL IN THE ART

Petitioner does not put forth a definition of a POSA in the Petition, but in their declarations, Drs. Buckton and Batchelor each put forth identical definitions. Ex.1002(Buckton Decl.), ¶17; Ex.1003(Batchelor Decl.), ¶16. For purposes of this

⁶ Petitioner argues that Applicant’s evidence of unexpected results lacks a nexus to the claims because the evidence is limited to certain doses and human patients. Pet., 17. Patent Owner disagrees but does not address that issue here because it is unnecessary for a finding that the Petition should not be instituted as set forth below.

Preliminary Response, Patent Owner does not currently dispute Drs. Buckton and Batchelor's proposed definition of a POSA. Patent Owner's expert, Dr. Corey Berkland, qualifies as a POSA under Petitioner's proposed definition.

Ex.2001(Berkland Decl.) at ¶¶2-15, 28-30. If a trial is instituted, Patent Owner reserves the right to submit a different POSA definition than that proposed by Drs. Buckton and Batchelor.

V. CLAIM CONSTRUCTION

Pursuant to 37 C.F.R. § 42.100(b), a claim in an IPR is construed using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. § 282(b). In an ongoing district court litigation involving the '628 patent, the court adopted Patent Owner's construction of "non-enteric-coated" as a formulation "that does not comprise a coating intended to release the active ingredient(s) beyond the stomach." Ex.2032(Celgene v. Accord 1:21-cv-01795-RGA Doc 40) at 1 (adopting the construction on the papers without oral argument). This construction is provided by the '628 patent itself. Ex.1001('628 patent), 11:42-45. Petitioner does not appear to dispute this construction. Pet., 20.

Additionally, in the ongoing district court litigation, Patent Owner agreed to construe the term "test subject" as "a human or other animal who received the

recited pharmaceutical composition in connection with a test of the recited parameter.” Ex.2045(Celgene v. Accord 1:21-cv-01795-RGA Doc 35), 3.

Petitioner does not appear to dispute this construction either. Pet., 20.

Petitioner alleges that claims 14 and 15 do not limit the scope of claim 13. Pet., 25-26. Claim 13 depends from independent claim 1 and recites “wherein the tablet comprises a sugar coating, a film coating, or a compression coating.” Ex.1001(’628 patent), claim 13. Claim 14 depends from claim 13 and recites “wherein the film coating is a cellulose ether polymer.” *Id.*, claim 14. Claim 15 depends from claim 14 and limits the cellulose ether polymer to specific species. *Id.*, claim 15. Petitioner asserts that claims 14 and 15 “do not limit the scope of Claim 13 to the ‘film coating’ species, which means that all three species are still claimed in the alternative.” Pet., 25-26. Patent Owner disagrees. However, as shown in this Preliminary Response, Petitioner cannot demonstrate that it is reasonably likely to prevail in establishing the unpatentability of challenged claim 1 upon which claims 14 and 15 ultimately depend. If a trial is instituted, Patent Owner reserves the right to submit a different claim construction for claims 14 and 15 than that proposed by Petitioner.

VI. THE ASSERTED REFERENCES

A. Ionescu

Ionescu “relates to the isolation of crystalline polymorphic and pseudopolymorphic forms of 5-azacytidine....” Ex.1004-0003(Ionescu), 1:8-10; Ex.2001(Berkland Decl.) at ¶37. Ionescu discloses that “[i]t is an object of the present invention to characterize the polymorphic forms of 5-azacytidine.” Ex.1004-0004(Ionescu), 2:7-9; Ex.2001(Berkland Decl.) at ¶37.

Ionescu discloses that “5-azacytidine exists in at least eight different polymorphic and pseudopolymorphic crystalline forms (Forms I-VIII), in addition to an amorphous form” and provides their X-ray powder diffraction patterns and methods for synthesizing several of these forms. Ex.1004-0004(Ionescu), 2:11-14, 2:23-26; -0005-0014, 3:7-12:10; -0017-0024, 15:5-22:26; Figs. 1-8; Ex.2001(Berkland Decl.) at ¶38.

Ionescu notes that 5-azacytidine may be used in treating diseases such as MDS (Ex.1004-0003(Ionescu), 1:10-11; Ex.2001(Berkland Decl.) at ¶39) and provides a general disclosure that the forms of 5-azacytidine may be used in a pharmaceutical composition with one or more pharmaceutically acceptable excipients, diluents, or carriers. Ex.1004-0002(Ionescu), 2:26-28; Ex.2001(Berkland Decl.) at ¶39. In describing pharmaceutical formulations,

Ionescu merely discloses a generic list of many different types of pharmaceutical formulations. Ex.1004-0014-0016(Ionescu), 12:11-14:29; Ex.2001(Berkland Decl.) at ¶39. Ionescu separately notes, without referring to any particular embodiment or formulation and without further guidance, that “[t]he compositions of the invention can be formulated so as to provide quick, sustained, controlled, or delayed release of the drug substance after administration to the patient by employing procedures well known in the art.” Ex.1004-0015(Ionescu), 13:7-10; Ex.2001(Berkland Decl.) at ¶39.

B. Atadja

Atadja “relates to a combination which comprises (a) one or more chemotherapeutic agents and (b) a histone deacetylase inhibitor...especially for use in the treatment of proliferative diseases,” “pharmaceutical compositions comprising such a combination,” “a method of preventing or treating proliferative diseases...with such a combination,” and “a commercial package or product comprising such a combination” and describes the histone deacetylase inhibitors and their structures. Ex.1005-0001(Atadja), Abstract; -0010-0023, 9:15-22:5; Ex.2001(Berkland Decl.) at ¶40. For the chemotherapeutic agents, Atadja states that “[p]referably, the compounds or the pharmaceutically acceptable salts thereof, are administered as an oral pharmaceutical formulation in the form of a tablet,

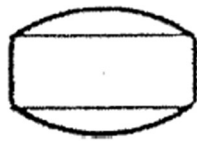
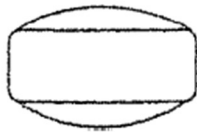
capsule or syrup; or as parenteral injections if appropriate.” Ex.1005-0028(Atadja), 27:16-18; Ex.2001(Berkland Decl.) at ¶40. Atadja also discloses that “‘chemotherapeutic agent(s)’ is [] broad” (Ex.1005-0003(Atadja), 2:23; Ex.2001(Berkland Decl.) at ¶40) and includes a laundry list of compounds. Ex.1005-0004(Atadja), 3:1-24 (providing a list of types of compounds); *see also* Ex.1005-0004-0010(Atadja), 3:25-9:14 (providing specific examples of chemotherapeutic agents); Ex.2001(Berkland Decl.) at ¶40. Atadja refers to 5-azacytidine as one possible chemotherapeutic option out of a list of dozens for administration with a histone deacetylase inhibitor. *See, e.g.*, Ex.1005-0027-0028(Atadja), 26:28-27:16; Ex.2001(Berkland Decl.) at ¶40.

C. Gibson

Gibson is a general reference textbook that is cited in the ’628 patent specification and is “intended to be a practical guide to pharmaceutical preformulation and formulation” that “can be used as a reference source and a guidance tool for those working in the pharmaceutical industry or related industries....” Ex.2042(Gibson Supplemental), 1; Ex.1001(’628 patent), 37:24-32; Ex.2001(Berkland Decl.) at ¶41. Gibson discloses that “[s]pecial considerations and issues for the formulation development for each route [of administration] and type of dosage form are discussed....” Ex.2042(Gibson Supplemental), 11;

Ex.2001(Berkland Decl.) at ¶41. Gibson describes that oral solid dosage forms may be sugar-coated through a “multistep process” typically employing a seal coat, a subcoat, and a smoothing coat (Ex.1006-0062(Gibson); Ex.2001(Berkland Decl.) at ¶¶41, 51) as depicted in Figure 11.24 reproduced below.

Figure 11.24 Stages of sugar coating.



Sealing coat.



Subcoat—rounds off edges.



**Smoothing coat – adds bulk to the tablet.
Contains colorants where applicable.**

Ex.1006-0063(Gibson). “One of the reasons for [sugar] coating tablets is to protect the drug substances from environmental factors such as moisture,” and the sealing coat ensures that coating solutions do not penetrate into the core. Ex.1006-0063(Gibson); Ex.2001(Berkland Decl.) at ¶41. Gibson discloses both enteric coated and non-enteric coated tablets (*see, e.g.*, Ex.1006-0068(Gibson); Ex.2001(Berkland Decl.) at ¶41), and notes that sugar-coated tablets may be used with an enteric coating. Ex.1006-0070(Gibson) (“The original enteric coating material [shellac], originally used in sugar-coated tablets.”); Ex.2001(Berkland Decl.) at ¶41. Gibson also discloses that “[t]he most common type of modified release coating is the enteric coat that is designed to prevent release of the drug substance in the stomach because the drug is either irritant to the gastric mucosa or it is *unstable in the gastric juice*.” Ex.1006-0068(Gibson), 439; Ex.2001(Berkland Decl.) at ¶41. Gibson does not mention 5-azacytidine or any treatment of MDS or AML.

D. Pharmion-PR

Pharmion-PR is a press release from the predecessor company to Patent Owner where the inventors began their work on oral azacytidine formulations. Pharmion-PR provides high level results of a study designed to assess the safety, tolerability, and pharmacokinetics of escalating single doses of orally administered

5-azacytidine in patients with MDS, AML, or solid tumors. Ex.1010-0005(Pharmion-PR); Ex.2001(Berkland Decl.) at ¶42. Pharmion-PR discloses that the study concluded and a subsequent multi-dose escalating study of oral 5-azacytidine was being performed. Ex.1010-0005(Pharmion-PR); Ex.2001(Berkland Decl.) at ¶42. Pharmion-PR does not disclose the formulation of 5-azacytidine employed in either study.

VII. THE BOARD SHOULD DENY INSTITUTION OF GROUND 1 BECAUSE PETITIONER HAS FAILED TO DEMONSTRATE A REASONABLE LIKELIHOOD THAT THE CHALLENGED CLAIMS ARE ANTICIPATED UNDER 35 U.S.C. § 102(b)

The Petition fails to establish a reasonable likelihood that Petitioner will prevail on at least one of the challenged claims. Ex.2001(Berkland Decl.), ¶43. Petitioner has failed to show that all limitations of independent claims 1 or 28 are disclosed in the Ionescu reference cited in the Petition (Ground 1). Ex.2001(Berkland Decl.), ¶44. For at least this reason, the Ground 1 also fails with respect to the challenged dependent claims. Ex.2001(Berkland Decl.), ¶¶34- 36.

A. Ionescu Fails to Disclose A Non-Enteric Coated Tablet as Required by All of The Claims Challenged in Ground 1

Both independent claims of the '628 patent—claim 1 and claim 28—require “a non-enteric coated tablet.” Ex.1001('628 patent), claims 1, 28. Petitioner has failed to establish that Ionescu discloses a non-enteric coated tablet. Thus, the

Petition fails to demonstrate that the challenged independent and dependent claims are anticipated by Ionescu. Ex.2001(Berkland Decl.) at ¶48.

1. Petitioner fails to establish that Ionescu discloses “a non-enteric-coated tablet”

a. Ionescu’s disclosure that tablets may be coated with sugar does not disclose a type of coating that determines the release profile of the tablet

In its analysis of element 1(d) and claim 28⁷, Petitioner states “the sugar-coated tablets of Ionescu are NEC [non-enteric coated]....” Pet., 22. Petitioner’s analysis is incorrect and unsupported.

As described by the ’628 patent and adopted by the District Court, a “non-enteric-coated” formulation is one “that does not comprise a coating intended to release the active ingredient(s) beyond the stomach....” Ex.1001(’628 patent), 11:42-45; Pet., 20; Ex.2032(Celgene v. Accord 1:21-cv-01795-RGA Doc 40) at 1; Ex.2001(Berkland Decl.) at ¶49.

Petitioner’s own cited art makes clear that sugar coatings are different coatings used for a different purpose than controlling the release profile of the drug. Ex.2001(Berkland Decl.) at ¶50. Instead, sugar coatings are used to produce

⁷ Petitioner relies on the 1(d) analysis for the similar limitation in claim 28. Pet., 23.

an “[e]legant final product,” “for identification purposes,” and to provide “protection from [the] environment” (Ex.1006-0072(Gibson); Ex.2001(Berkland Decl.) at ¶50) including protection from moisture, air, and light. Ex.1006-0062(Gibson); Ex.2001(Berkland Decl.) at ¶50; *see also* Ex.1030-0009(Remington) (disclosing sugar coatings “may be colored and are beneficial in covering up drug substances possessing objectionable tastes or odors and in protecting materials sensitive to oxidation.”); Ex.2001(Berkland Decl.) at ¶50. That is, a POSA would recognize that the purposes of sugar coatings are different from and unrelated to the purposes for employing an enteric or non-enteric coated tablet formulation. Ex.2001(Berkland Decl.) at ¶50.

Petitioner’s references disclose that sugar coating is one of the major and oldest techniques for applying coatings to a pharmaceutical dosage form and requires a “multistep process” resulting in “a sugar coating...consist[ing] of three types of coat: a sealing coat, a subcoat and a smoothing coat.” Ex.1006-0062(Gibson), -0063; *see also* Ex.1030-0047(Remington); Ex.2001(Berkland Decl.) at ¶51. Further, Gibson lists sugar coating among the “main methods used to coat pharmaceutical tablets,” but is entirely silent as to the specific release profile of the active ingredient from tablets coated with sugar. Gibson Ex.1006-0062(Gibson); *see also* Ex.1030-0047(Remington) (disclosing the “major

techniques for applying coatings to pharmaceutical solid dosage forms [are] (1) sugar coating, (2) film coating, (3) microencapsulation and (4) compression coating.”); Ex.2001(Berkland Decl.) at ¶51.

Thus, the use of a sugar coating would **only** inform a POSA that a formulation is a certain type of multilayered formulation without providing any information regarding the release profile of the formulation. Ex.2001(Berkland Decl.) at ¶52. As such, a POSA would have understood a tablet with a sugar coating does not mean that it is a non-enteric coated tablet. Ex.2001(Berkland Decl.) at ¶52. A POSA would need more information to determine whether it is non-enterically coated. Ex.2001(Berkland Decl.) at ¶52. Indeed, Petitioner fails to address the evidence cited in its own exhibits and throughout the literature clearly demonstrating that the disclosure by Ionescu of a tablet that may be coated with sugar—Petitioner’s “sugar-coated tablet” (*see, e.g.*, Pet., 22; Ex.1002(Buckton Decl.), ¶83)—provides no teaching whatsoever of a non-enteric coated tablet formulation of 5-azacytidine. Pet., 22-23; *see also* Ex.1006-0070(Gibson); Ex.1030-0047(Remington), -0049-0050; VII.A.1, VIII.A., VIII.B; Ex.2001(Berkland Decl.) at ¶52.

In fact, the sealing coat of a sugar-coated tablet can be an enteric coating or non-enteric coating, which Petitioner fails to address. Ex.2001(Berkland Decl.) at

¶53. As discussed in the literature and explained by Dr. Berkland, a sealing coat is applied during sugar coating, which may be enteric coated to make a delayed release tablet. *See, e.g.*, Ex.1006-0070(Gibson), -0068; Ex.2001(Berkland Decl.) at ¶53. Indeed, this fact is well established and is supported by Petitioner’s own exhibits. For example, Remington explains, “If an enteric-coated [sugar-coated] product is required, additional quantities of the seal-coat solution are applied” or “synthetic polymers such as polyvinyl acetate phthalate or cellulose acetate phthalate”—both of which are enteric coatings—are used. Ex.1030-0047(Remington), -0049-0050; Ex.2028(Remington 2005), 889, 930; Ex.2001(Berkland Decl.) at ¶53; *see also* Ex.1006-0063(Gibson), Figure 11.24 (depicting the sugar-coating process of employing a sealing coat, a subcoat, and a smoothing coat).

Additional foundational literature in the field also makes clear that a POSA would not understand a disclosure of the use of a sugar coating with no further guidance to disclose a non-enteric coated tablet. Ex.2001(Berkland Decl.) at ¶54. For example, Lieberman, a pharmaceutical formulation textbook, states that the first stage of the “sugar-coating process” is sealing to ensure “product stability (both physical and chemical)” “and to prevent some tablet core ingredients from migrating into the coating....” Ex.2020(Lieberman), 79-80; *see also* Ex.1030-

0047(Remington); Ex.1006-0063(Gibson); Ex.2028(Remington 2005), 930; Ex.2001(Berkland Decl.) at ¶54. Lieberman also notes that “if the final product is to have enteric properties, this result is usually achieved by using one of the enteric polymers (such as PVAP or CAP) as the basis for the seal coat and ensuring that sufficient coating material is applied.” Ex.2020(Lieberman), 79-80; Ex.2001(Berkland Decl.) at ¶54. The next step is to deposit sugar (*e.g.*, in the smoothing coat) on top of this enteric or non-enteric sealing coat. Ex.2020(Lieberman), 79, 83; Ex.2028(Remington 2005), 930-931; Ex.2001(Berkland Decl.) at ¶54. Therefore, a POSA would have understood that the presence of a sugar coat provides no information as to whether the formulation is enterically coated or non-enterically coated. Ex.2001(Berkland Decl.) at ¶55. A POSA would need more information to make that determination. Ex.2001(Berkland Decl.) at ¶55. Because the mere disclosure of a sugar coat is entirely independent from and sheds no light on the use of a non-enteric coating, Petitioner fails to establish that Ionescu discloses a non-enteric coated tablet formulation of 5-azacytidine as claimed. Ex.2001(Berkland Decl.) at ¶55.

Petitioner attempts to buttress its faulty conclusion that “[a]t least the sugar-coated tablets of Ionescu are NEC [non-enteric coated]” by improperly equating the disclosure of the use of sugar coatings with Ionescu’s separate disclosure that

compositions can be formulated to provide a “quick” release. Pet., 22; Ex.2001(Berkland Decl.) at ¶56. However, Petitioner mischaracterizes the reference because Ionescu’s disclosure of “quick” release as a possible formulation is in a separate paragraph from its mention of sugar coatings, the paragraph fails to mention any tablet formulations, and nowhere does Ionescu state, suggest, or indicate that a sugar coating would result in a “quick” release or any other type of release. Ex.1004(Ionescu), 12:7-13:21; Ex.2001(Berkland Decl.) at ¶56. Further, the Petition does not acknowledge that Ionescu discusses “controlled” and “delayed” releases in the same sentence as “quick” release (Ex.1004(Ionescu), 13:7-10; Ex.2001(Berkland Decl.) at ¶56), as well as other formulations, including sterile injectable solutions, elsewhere. Ex.1004(Ionescu), 12:22-25; Ex.2001(Berkland Decl.) at ¶56.

In sum, Ionescu’s disclosure that tablets may be coated with sugar does not disclose a pharmaceutical formulation of 5-azacytidine in a non-enteric coated tablet, and Petitioner fails to explain how a POSA would have understood Ionescu as disclosing such a non-enteric coated tablet formulation. Pet., 22-23; Ex.2001(Berkland Decl.) at ¶¶56, 58. Thus, the Petition fails to establish a reasonable likelihood that Ionescu anticipates the independent claims and all challenged dependent claims in Ground 1. Ex.2001(Berkland Decl.) at ¶58.

- b. Based on the prior art, a POSA in December 2008 would at most have understood that to the extent any 5-azacytidine tablets were coated with sugar, as disclosed in Ionescu, such tablets would be enterically coated tablets*

Petitioner also fails to address that a POSA in December 2008 would have understood that a sugar-coated tablet of 5-azacytidine would have been an enterically coated tablet. Pet., 22-23; Ex.2001(Berkland Decl.) at ¶57. “[T]he dispositive question regarding anticipation [i]s whether *one skilled in the art* would reasonably understand or infer from the [prior art reference’s] teaching’ that every claim element was disclosed in that single reference.” *Dayco Prod., Inc. v. Total Containment, Inc.*, 329 F.3d 1358, 1368 (Fed. Cir. 2003) (original emphasis) (internal citations omitted). Further, “[a]mbiguous references do not anticipate a claim” as “a single reference” is required to “describe the claimed invention *with sufficient precision and detail* to establish that the subject matter existed in the prior art.” *Wasica Fin. GmbH v. Cont’l Auto. Sys.*, 853 F.3d 1272, 1284 (Fed. Cir. 2017) (citing *Verve LLC v. Crane Cams Inc.*, 311 F.3d 1116, 1120 (Fed. Cir. 2002)) (original emphasis).

As Dr. Berkland explains, a POSA would have understood that a sugar-coated tablet of 5-azacytidine would be an *enteric* sugar-coated tablet to avoid the

known degradation challenges presented by oral administration of 5-azacytidine.

Ex.2001(Berkland Decl.), ¶¶57, 64-85.

First, a POSA would have understood that 5-azacytidine suffered from instability and rapidly hydrolyzes, especially in acidic environments like the stomach. *See* II.A.2; Ex.2001(Berkland Decl.) at ¶¶66, 68-78. Indeed, this fact *is not disputed*. Both of Petitioner’s experts acknowledge this, but they fail to account for these teachings when arriving at their conclusions. Ex.1002(Buckton Decl.), ¶¶55, 119 (citing Ex.1014(Chan) and stating, “Such degradation data for 5-azacytidine was known and reported in the literature.”); Ex.1003(Batchelor Decl.), ¶¶27, 34-35; Ex.2001(Berkland Decl.) at ¶¶68, 76. By 2008, a POSA would have understood 5-azacytidine’s degradation in acidic environments to have been firmly established. For example, by the early 1960s, it was known that “in acidic media, 5-azacytidine is readily cleaved.” Ex.2027(Pitřhová), 2809; *see also* Ex.2012(Čihák), 2093, 2096, 2097; Ex.2024(Notari), 1153; Ex.1014(Chan), 807; Ex.2021(Lin), 1230; Ex.2019(Kissinger), 309-310; Ex.2029(Stresemann), 8; Ex.2011(Cheung), 1187; Ex.1042-0005(IARC); Ex.2041(WO2008/028193), ¶[0007]; Ex.2001(Berkland Decl.) at ¶¶68-69. Additionally, art before the PTO states “[a]zacytidine presents several significant challenges...including sub-optimal physiochemical characteristics, hydrolytic instability, and active enzymatic

degradation” which are “all non-conducive to high passive intestinal tract absorption,” and so 5-azacytidine “must be formulated to avoid the chemical and enzymatic degradation occurring presystemically.” Ex.1034-0001(Stoltz); *see also* Ex.2017(Gaubert), 837-838; Ex.2041(WO2008/028193), ¶¶0007]; Ex.2001(Berkland Decl.) at ¶72. A POSA would have understood that “[a]zanucleoside drugs” such as 5-azacytidine were “widely considered to be unstable, and ha[d] therefore been handled with considerable care, both in the laboratory and in the clinic” and that the acidic degradation of 5-azacytidine “interferes with a potential oral administration of these drugs.” Ex.2029(Stresemann), 8; *see also* Ex.2023(National Cancer Institute), 3-4; Ex.2011(Cheung), 1159; Ex.1042-0005(IARC); Ex.2022(Mund), 8; Ex.2044(WO2004/082618), 1:28, 4:5-6; Ex.2001(Berkland Decl.) at ¶¶68, 70, 71. These known stability issues led many to investigate alternatives to 5-azacytidine. Ex.2004(Beisler), 282; Ex.2003(Aparicio), 631; Ex.2001(Berkland Decl.) at ¶74. Thus, in 2008 a POSA would have understood that 5-azacytidine was expected to readily break down in harsh, acidic environments, such as the stomach, before it could be absorbed to provide a therapeutic effect. Ex.2001(Berkland Decl.) at ¶¶65, 67, 75.

In addition to acid hydrolysis, a POSA would have understood cytidine deaminase to degrade 5-azacytidine through a parallel metabolic pathway.

Ex.2001(Berkland Decl.) at ¶¶79-85. By at least 1987 “it [wa]s known that azacitidine is rapidly deaminated by cytidine deaminase which is present in...gastrointestinal epithelium” (Ex.2034(Glover), 738), located throughout the various organs of the gastrointestinal tract including the esophagus, stomach, small intestine, and large intestine. *See, e.g.*, Ex.2047(Savage). *See also* Ex.2012(Čihák), 2100; Ex.2009(Chabner), 2765; Ex.2001(Berkland Decl.) at ¶¶79, 82. By December 2008 a POSA would have understood that “[t]he poor bioavailability of such cytidine analogs [*e.g.*, 5-azacytidine] is presumably due to the degradation of the cytidine analog by cytidine deaminases as well as their inherent chemical instability in the acidic gastric environment.” Ex.1021(Sands), ¶[0012] (before the PTO); *see also* Ex.2017(Gaubert), 837-838; Ex.2010(Chen), 21; Ex.2001(Berkland Decl.) at ¶81. The literature reported that 5-azacytidine is absorbed in the gastrointestinal tract where enzymatic metabolism is active.

Ex.2041(WO2008/028193), ¶¶[0024]-[0025]; Ex.2001(Berkland Decl.) at ¶82. Therefore, a POSA would have understood that cytidine deaminase also presented a challenge to developing non-enteric coated tablet formulations of 5-azacytidine because the drug would have been released in the stomach and degraded in the

gastrointestinal tract before a therapeutically effective amount of the drug could be absorbed. Ex.2001(Berkland Decl.) at ¶83.

Further, hydrolysis and enzymatic metabolism were known to inhibit oral administration of unstable drugs generally:

The best drugs can't exert their beneficial effects if they are not reaching their target site in the body at an appropriate concentration and for a sufficient length of time....[T]his may also be the case after the tablet has been swallowed....Some drugs chemically or enzymatically degrade in the stomach....Some drugs cannot be delivered by the oral route as they are metabolised in the liver, before reaching the systemic circulation.

Ex.2016(FASTtrack), viii; Ex.2001(Berkland Decl.) at ¶64; *see also*

Ex.2043(Lieberman Vol. 2), 352-53. Since 5-azacytidine was known to be susceptible to degradation via both hydrolysis and enzymatic degradation (Ex.2017(Gaubert), 837-838; Ex.2034(Glover), 738), a POSA would have understood these known challenges to be roadblocks to formulating a non-enteric coated 5-azacytidine tablet, which releases the drug in the stomach.

Ex.2001(Berkland Decl.) at ¶¶75-78, 83-85. Thus, even if a POSA were to infer a release profile from the sugar coating disclosed in Ionescu, *at most* a POSA would have understood the tablet to be an enteric coated, delayed release tablet coated

with sugar to avoid degradation of the compound in the acidic, aqueous conditions of the stomach. Ex.2001(Berkland Decl.) at ¶¶67, 75-78, 83-85.

Petitioner's analysis of element 1(d) is entirely silent as to how a POSA would have understood the Ionescu reference given the known issues with degradation of 5-azacytidine. Pet., 22-23; Ex.2001(Berkland Decl.) at ¶58. The Petition does not explain why a POSA would have understood Ionescu's disclosure that tablets may be coated with sugar as disclosing a non-enteric coated tablet in view of the undisputed concern regarding hydrolysis of the compound in the stomach, and nowhere does it address the known issue of enzymatic degradation. Ex.2001(Berkland Decl.) at ¶¶57, 76-77, 84.

For these reasons, Petitioner has failed to establish that Ionescu discloses a non-enteric coated tablet of 5-azacytidine and there is no reasonable likelihood that Petitioner will prevail on Ground 1.

VIII. THE BOARD SHOULD DENY INSTITUTION OF GROUNDS 2 AND 3 BECAUSE PETITIONER HAS FAILED TO DEMONSTRATE A REASONABLE LIKELIHOOD THAT THE CHALLENGED CLAIMS ARE OBVIOUS UNDER 35 U.S.C. § 103(A)

The Petition fails to establish a reasonable likelihood that Petitioner will prevail on its obviousness grounds (Grounds 2-3) for at least one of the challenged claims. Ex.2001(Berkland Decl.) at ¶¶43, 45.

Independent claims 1 and 28 of the '628 patent require “a non-enteric coated tablet.” Ex.1001('628 patent), claims 1, 28. As discussed above, Petitioner has failed to demonstrate that this limitation is disclosed in Ionescu. *See* VII.A; Ex.2001(Berkland Decl.) at ¶44. Petitioner further fails to establish that “a non-enteric coated tablet” is rendered obvious by Ionescu in combination with the other cited references (*i.e.*, Atadja, Gibson, and the knowledge of a POSA (Ground 2) or Atadja, Gibson, Pharmion-PR, and the knowledge of a POSA (Ground 3)). None of Atadja, Gibson, Pharmion-PR, or knowledge of a POSA disclose “a non-enteric coated tablet” of 5-azacytidine, and so all of the secondary references fail to overcome the deficiency of Ionescu. *See* VIII.A. Because the challenged dependent claims all depend from claims 1 or 28, they are also not obvious over Ionescu in combination with the cited secondary references. Ex.2001(Berkland Decl.) at ¶¶34-36.

The Petition fails to establish a reasonable likelihood that Petitioner will prevail on its obviousness grounds. **First**, Petitioner has failed to show that all limitations of independent claims 1 or 28 are disclosed in or rendered obvious by the references cited in the Petition (Grounds 2-3). Ex.2001(Berkland Decl.) at ¶¶59, 63. **Second**, Petitioner’s obviousness analysis fails to establish that a POSA would have had a reasonable expectation of success in arriving at the invention

claimed in claims 1 or 28 or the challenged dependent claims. Ex.2001(Berkland Decl.) at ¶¶45, 64-85.

A. Petitioner Fails to Establish That The Art Cited in Grounds 2 and 3 Discloses The Limitation “Wherein The Composition Is A Non-Enteric Coated Tablet” of Independent Claims 1 and 28

In Grounds 2 and 3, Petitioner does not rely on any of the secondary references as disclosing a non-enteric coated tablet formulation of 5-azacytidine, instead relying on Ionescu as allegedly teaching this limitation. Pet., 31-32 (stating “Ionescu teaches NEC [non-enteric coated] tablets of 5-azacytidine,” and referencing anticipation), 58-62. In Ground 2, the Petition relies on Atadja only as allegedly teaching an oral tablet formulation of 5-azacytidine thereby not only mischaracterizing Atadja (*see* VIII.B), but also adding nothing over the alleged teaching of Ionescu. Pet., 32. Gibson is only cited to teach the general concept that oral and non-enteric coated dosage forms were the default and most preferred forms, but it does not address 5-azacytidine specifically. Pet., 32. Ground 3 adds the Pharmion-PR reference, but it is relied upon only to provide a motivation to select a non-enteric coated tablet from the other formulations in Ionescu and Atadja and not for disclosure of a non-enteric coated tablet. Pet., 59-60. Thus, Petitioner fails to identify any disclosure in that the secondary references that

remedies the failure of Ionescu to disclose a non-enteric coated tablet formulation of 5-azacytidine. Ex.2001(Berkland Decl.) at ¶¶59-63.

B. Petitioner Fails to Establish A Reasonable Expectation of Success

Petitioner's obviousness grounds also fail to establish that a POSA would have had a reasonable expectation of success in developing a non-enteric coated tablet of 5-azacytidine that would deliver a therapeutically effective amount of the drug to a patient. In both Ground 2 and Ground 3, Petitioner attempts to establish obviousness based on alleged motivations to combine and obvious to try theories. *See* Pet., 31-38, 58-62. In doing so, Petitioner disregards the known instability of the drug and relies upon mischaracterizations of the secondary references for alleged motivation to do something that the knowledge of a POSA would counsel against—administering 5-azacytidine orally without a protective enteric coating. Pet., 31-62; *see also* Ex.2001(Berkland Decl.) at ¶¶64-85.

For something to be obvious to try, it requires choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007). Where there is uncertainty in a field, “it [i]s [the challenger’s] burden to demonstrate that despite any unpredictability in the literature, a skilled artisan nevertheless would have had a reasonable expectation of success.” *Eli Lilly & Co. v. Teva Pharm. Int'l GmbH*, 8

F.4th 1331, 1349 (Fed. Cir. 2021) (finding no reasonable expectation of success where the literature attested to “uncertainty, unpredictability, and skepticism” in the field). Further, “[u]npredictability of results equates more with nonobviousness rather than obviousness.” *Honeywell Int’l Inc. v. Mexichem Amanco Holding S.A. De C.V.*, 865 F.3d 1348, 1356 (Fed. Cir. 2017).

Given the state of the art in December 2008, a POSA would not have had a reasonable expectation of success in developing a non-enteric coated tablet comprising a therapeutically effective amount of 5-azacytidine. As discussed above, a POSA would have understood that the compound would be degraded before it could be absorbed to provide a therapeutic benefit. Ex.2001(Berkland Decl.) at ¶¶64-85. Again, ***this is not in dispute***. It was well known that non-enteric coated tablets release the drug in the stomach where, as acknowledged by Petitioner’s experts, 5-azacytidine would be degraded. Ex.1002(Buckton Decl.), ¶119; Ex.1003(Batchelor Decl.), ¶¶34-35; Ex.2001(Berkland Decl.) at ¶¶49, 67. Indeed, Petitioner’s experts note that degradation should be accounted for (Ex.1002(Buckton Decl.), ¶55; Ex.1003(Batchelor Decl.), ¶¶27, 34-35, 46; Ex.2001(Berkland Decl.) at ¶¶68, 71, 72, 76-77), but then the Petition fails to address this very issue in its obviousness analysis. In fact, the Petition provides ***no*** expert analysis as to why there would have been a reasonable expectation of

success in arriving at the claimed non-enteric coated tablet of 5-azacytidine in view of the known challenges of administering 5-azacytidine such that it is exposed to the stomach environment. Pet., 38, 61-62; Ex.2001(Berkland Decl.) at ¶¶76-77.

The Petition relies on attorney argument that “knowledge in the art that 5-azacytidine was orally bioavailable and well tolerated” would have provided a reasonable expectation of success in arriving at a non-enteric coated tablet of 5-azacytidine. Pet., 38, 61. However, the Petition does not cite any evidence or expert testimony for support, and the argument misses the point. As previously discussed and supported by Petitioner’s own evidence, a POSA as of December 2008 would have understood that 5-azacytidine would be orally bioavailable only if it were protected from degradation using an enteric coating, and thus a therapeutically effective amount of the drug would be absorbed.

Ex.2001(Berkland Decl.) at ¶¶57, 77, 83. This does not provide a POSA with a reasonable expectation of success for a *non*-enteric coated tablet of 5-azacytidine. For this reason alone, the obviousness analysis fails. Ex.2001(Berkland Decl.) at ¶¶78, 85.

Petitioner’s additional argument that the disclosures of Ionescu, the secondary references, and the “knowledge in the art” provide a reasonable expectation of success mischaracterizes the art. Pet., 38. As described with

respect to Ground 1 (*see* VII.A.1) and incorporated by reference here, Ionescu does not disclose “oral administration of NEC [non-enteric coated] tablets of 5-azacytidine to treat MDS....” Pet., 38; Ex.2001(Berkland Decl.) at ¶¶48-56. Nor can Petitioner demonstrate that Ionescu renders the claims obvious to try. Pet., 37-38. Petitioner provides no analysis as to why such a non-enteric coated formulation is predictable and would provide a reasonable expectation of success in view of the voluminous art establishing that 5-azacytidine, if released in the stomach, would rapidly breakdown. Ex.2001(Berkland Decl.) at ¶¶65-78.

Petitioner’s reliance on Atadja is also misplaced and mischaracterizes the reference. Pet., 33, 37. The Petition does not cite any expert testimony to support this argument, and the reasoning is flawed. *Id.*

First, Atadja’s disclosure is not specific to 5-azacytidine, but instead directed towards many different chemotherapeutic agents and histone deacetylase inhibitors. *See, e.g.*, Ex.1005(Atadja), 1-9; Ex.2001(Berkland Decl.) at ¶60.

Second, the Petition quotes only part of Atadja’s disclosure regarding drug administration options. Atadja generally discusses administration options for a variety of chemotherapeutic agents and states, “Preferably, the compounds or the pharmaceutically acceptable salts thereof, are administered as an oral pharmaceutical formulation in the form of a tablet, capsule or syrup; *or as*

parenteral injections if appropriate.” Ex.1005(Atadja), 27. A POSA reading Atadja in December 2008 would have understood parenteral injection to be the only administration of 5-azacytidine approved by the FDA. Ex.1007(Vidaza[®] Label 2004); Ex.1008(Vidaza[®] Label 2007); Ex.2001(Berkland Decl.) at ¶60. By repeatedly excluding this final clause, both Petitioner (*see* Pet., 32) and Dr. Buckton (*see* Ex.1002(Buckton Decl.), ¶¶40-42) improperly suggest oral formulations are the sole focus of Atadja.

However, as Dr. Berkland explains, a POSA reading Atadja would have understood that certain agents disclosed may have been administered as tablet or syrup, but that 5-azacytidine would be administered as a parenteral injection given that this method of administration was FDA-approved and in view of the known challenges with the drug. Ex.2001(Berkland Decl.) at ¶60. Thus, as Dr. Berkland recognizes, a POSA in December 2008 would not have had a reasonable expectation of success in formulating 5-azacytidine in a non-enteric coated tablet, and nothing in Atadja’s disclosure of methods of administering chemotherapeutic agents changes that. Ex.2001(Berkland Decl.) at ¶60; *see also id.* at ¶¶64-85. The Petition fails to provide evidence to support its attorney argument or to address the references cited by Dr. Berkland describing the challenges with formulating 5-

azacytidine as claimed.

In describing Gibson—which, as discussed above, does not provide any disclosure of 5-azacytidine or formulations thereof—Petitioner characterizes non-enteric coatings as the default formulation choice. Pet., 11, 12, 32, 36; Ex.2001(Berkland Decl.) at ¶61. However, in doing so, Petitioner omits any acknowledgement of the challenges with formulating a non-enteric coated tablet of 5-azacytidine, as described above and recognized by Petitioner’s experts and by Dr. Berkland. Ex.1002(Buckton Decl.), ¶55; Ex.1003(Batchelor Decl.), ¶¶27, 34-35, 46; Ex.2001(Berkland Decl.) at ¶¶64-85. Further, Petitioner dismisses enteric coatings because “there was no evidence that 5-azacytidine caused irritation of the gastric mucosa” (Pet., 13), but entirely fails to address that Gibson reports another reason for using an enteric coat that is present here: “because the drug...is unstable in gastric juice.” (Ex.1006-0068(Gibson); Ex.2001(Berkland Decl.) at ¶61).

Finally, Petitioner fails to explain how the mere disclosure that 5-azacytidine was “well-tolerated and quantifiable in plasma” in Pharmion-PR (Ex.1010-0005) would provide a POSA with a reasonable expectation of success in formulating a non-enteric coated tablet when the formulation used is not disclosed. Pet., 35-38, 58-62. Even assuming that a POSA would have been motivated to make an oral tablet of 5-azacytidine based on Petitioner’s arguments, Petitioner fails to address

that a POSA would have formulated an enteric coated tablet composition—not a non-enteric coated tablet composition—to protect the 5-azacytidine from degradation resulting from exposure to the stomach environment, as discussed above. *See* VII.A.1.b; *see also* Ex.2001(Berkland Decl.) at ¶62.

At least for these reasons, Petitioner has not established claims 1 and 28 or any claims dependent therefrom are obvious over Ionescu in view of Atadja, Gibson, and the knowledge of a POSA (Ground 2) or over Ionescu in view of Pharmion-PR, Atadja, Gibson, and the knowledge of a POSA (Ground 3). Ex.2001(Berkland Decl.) at ¶¶59-63.

IX. THIS PETITION WOULD MERIT DISCRETIONARY DENIAL OF GROUNDS 1-3 PURSUANT TO 35 U.S.C. § 325(D)

This Petition merits discretionary denial under §325(d) because Petitioner advances the same or substantially the same art and arguments that were previously presented to the Office and has not demonstrated the Examiner erred in a manner material to patentability when allowing the challenged claims to issue.

First, the same or substantially the same art and arguments were previously presented to the Office. The Examiner considered Ionescu, multiple substantively identical forms of the same disclosure, and an ISR presenting substantially the same argument as Petitioner’s argument regarding Ionescu. Additionally, the

disclosures relied upon in the Secondary References are substantially the same as art considered by the Office.

Second, the Examiner did not err when considering Ionescu. Ionescu does **not** disclose non-enteric coated tablets of 5-azacytidine, and a POSA at most would have understood oral 5-azacytidine tablet formulations to be enteric coated tablets. Additionally, Petitioner's reliance upon *Lyft v. Rideshare Displays*, No. IPR2021-01601, Paper 7 (P.T.A.B. Apr. 11, 2022) (non-precedential) is misplaced since *Lyft* is distinguishable. Further, Petitioner's experts' declarations and modelling do not provide new information that was not before the Examiner and overcome during prosecution. Thus, Petitioner is unable to point to anything that suggests the Examiner erred in properly determining that the prior art does not disclose or render obvious a therapeutically effective non-enteric coated tablet of 5-azacytidine for oral administration.

The Board considers several factors when evaluating whether to exercise its discretion under Section 325(d), including: (a) the similarities and material differences between the asserted art and the prior art involved during examination; (b) the cumulative nature of the asserted art and the prior art evaluated during examination; (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection; (d) the

extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or Patent Owner distinguishes the prior art; (e) whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and (f) the extent to which additional evidence and facts presented in the Petition warrant reconsideration of the prior art or arguments. *Becton, Dickinson and Co. v. B. Braun Melsungen AG*, No. IPR2017-01586, Paper 8 at 18-28 (P.T.A.B. Dec. 15, 2017) (“Becton Dickinson”) (informative). As shown below, in this case, these factors support the Board exercising its discretion to deny institution under §325(d).

These factors are applied according to a two-part framework:

(1) whether the same or substantially the same art previously was presented to the [Patent] Office or whether the same or substantially the same arguments previously were presented to the Office; and (2) if either condition of first part of the framework is satisfied, whether the

[IPR] petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims.⁸

Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH, No.

IPR2019-01469, Paper 6 at 8 (P.T.A.B. Feb. 13, 2020) (precedential).

Moreover, “[i]f reasonable minds can disagree regarding the purported treatment of the art or arguments, it **cannot** be said that the Office erred in a

⁸ Factors (a), (b), (d) set forth in *Becton Dickinson* should be read broadly. For example, “during examination” should mean “presented to the Office during any proceeding, including prior AIA proceedings.” *Advanced Bionics*, Paper 6 at 10. The focus of factor (c) should be whether the Office erred in “the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection.” For example, “if the record of the Office’s previous consideration of the art is not well developed or silent, then a petitioner may show the Office erred by overlooking something persuasive under factors (e) and (f).” *Id.*, 10-11. On the other hand, “if the alleged error is a disagreement with a specific finding of record by the Office, then ordinarily the petitioner’s required showing of material error must overcome persuasively that specific finding of record.” *Id.*

manner material to patentability.” *Id.*, 9. At bottom, this framework reflects a commitment to defer to previous Office evaluations of the evidence of record unless material error is shown. *Id.*

A. Step 1 of *Advanced Bionics* Favors Denying Institution Under § 325(d) Because The Same or Substantially The Same Art or Arguments Were Previously Presented to The Office

1. The Examiner considered Ionescu and related disclosures

Ionescu’s disclosure was before the Examiner in multiple forms and was considered by the Examiner during prosecution. Not only did the Examiner consider Ionescu and art with substantially the same disclosure as Ionescu, but he also considered an ISR that (i) specifically identified the vast majority of Ionescu’s disclosures Petitioner now relies on and (ii) suggested how these portions would be relevant to pending claims that recited a non-enteric coated tablet of 5-azacytidine.

a. The Examiner considered Ionescu

Ionescu, International Pat. Appl. Pub. No. WO2004/082619, is Ex.1004 and is the primary reference in each of the Grounds. Applicant provided Ionescu to the Office in an IDS listing only four other references after the second Office Action (Ex.1022-1129(IDS submitted September 5, 2012)), and the Examiner considered Ionescu before issuing a third Office Action (Ex.1022-2027(IDS considered Aug. 24, 2013); Ex.1022-2017(Office Action dated Aug. 29, 2013)).

b. The Examiner considered Ionescu family members with substantially the same disclosure as Ionescu

Ionescu claims priority to U.S. Pat. Appl. No. 10/390,578 (Ex.1004, Cover), which issued as U.S. Pat. No. 6,887,855 (“Ionescu-855”). U.S. Pat. Appl. No. 11/052,615 is a divisional of Ionescu-855 and issued as U.S. Pat. No. 7,078,518 (“Ionescu-518”). Ex.2036(Ionescu-518), Cover. U.S. Pat. Appl. No. 11/458,365 is a continuation of Ionescu-518, published as U.S.20060247189 (“Ionescu-189”) and issued as U.S. Pat. No. 7,772,199 (“Ionescu-199”). Ex.2038(Ionescu-189), Cover; Ex.2037(Ionescu-199), Cover. U.S. Pat. Appl. No. 12/787,214 is a continuation of Ionescu-199 and published as U.S. Pub. No. US2010/0298253 (“Ionescu-253”). Ex.2039(Ionescu-253), Cover.

Ionescu is substantively identical to Ionescu-855. *See, e.g.*, Ex.1004(Ionescu), 12:11-14:31 (“Pharmaceutical Formulations”); Ex.2035(Ionescu-855), 7:60-9:56 (“Pharmaceutical Formulations”). Further, Ionescu-518, Ionescus-189, Ionescu-199, and Ionescu-253 reflect an unbroken chain of continuations and divisional applications, share the same specification

with Ionescu-855, and are also substantively identical to Ionescu.⁹ The Examiner considered each of these three U.S. Patents and two U.S. Patent Publications. Ex.1022-0185(IDS submitted April 2, 2010); Ex.1022-0707-0709(IDS considered July 19, 2011); Ex.1022-0735(IDS submitted December 1, 2011); Ex.1022-1100(IDS considered February 23, 2012). That is, besides Ionescu itself, the Examiner considered five other patent documents with substantively identical disclosures during prosecution.

c. An ISR considered by the Examiner cited an Ionescu family member

During prosecution, Applicant also disclosed to the Examiner an ISR for International Pat. Appl. No. PCT/US2009/002999 (the “’999 PCT”), which the Examiner considered. Ex.1022-0187(IDS submitted April 2, 2010); Ex.1022-0709(IDS considered July 19, 2011). The ’999 PCT and the ’628 Patent are part of the same family, claim priority to the same provisional application, and have substantively identical specifications. Ex.1001(’628 patent); Ex.2026(WO2009/139888). The ISR cited to U.S. Pat. Pub. No. US2004/0186065

⁹ As with Ionescu itself, as discussed above, none of these family members, nor any family member sharing the disclosure of Ionescu-855 discloses a non-enteric coated tablet formulation of 5-azacytidine.

(“Ionescu-065”), which is the publication of Ionescu-855 and thus also substantively identical to Ionescu. Ex.2030(Ionescu-065).

Petitioner’s argument with respect to Ionescu is substantially the same as the argument presented by the ISR and considered by the Examiner during prosecution of the ’213 application. First, the ISR cites to paragraphs [0046]-[0056] of Ionescu-065.¹⁰ Ex.1022-0634(ISR dated September 14, 2009). These paragraphs correspond *exactly* to the entire 82 lines of Ionescu’s “Pharmaceutical Formulations” section. Ex.1004(Ionescu), 12:11-14:31; Ex.2030(Ionescu-065), ¶¶[0046]-[0056]. This shared Pharmaceutical Formulations section, cited by both the ISR during prosecution and by Petitioner, makes up the lion’s share of the Petitioner’s arguments. *See* Pet., 20-62; *see also* Ex.1002(Buckton Decl.), ¶¶39-93. Second, the ISR identifies Ionescu-065 as relevant to claims of the ’999 PCT that recite non-enteric coated formulations and tablets of 5-azacytidine. Ex.1022-

¹⁰ An apparent clerical error in the ISR cites to “page 4, paragraph 46-page 51, paragraph 56” of Ionescu-065. Ex.1022-0634(ISR dated September 14, 2009).

However, it would have been readily obvious to the Examiner that these paragraphs are properly found on pages 4-5 and not pages 4-51. Ex.2030(Ionescu-065), 4-5.

0634(ISR dated September 14, 2009); Ex.2026(WO2009/139888), Claims.

Indeed, the '999 PCT and the claims of the '213 application originally before the Examiner share 64 claims. Ex.2026(WO2009/139888), claims 1-22, 33-39, 40-74; Ex.1022-0100-0105('213 Application), original claims 1-29, 31-65. For example, original claim 1 in both applications recites:

A pharmaceutical composition for oral administration comprising a therapeutically effective amount of 5-azacytidine, wherein the composition releases the 5-azacytidine substantially in the stomach following oral administration to a subject.

Ex.2026(WO2009/139888), claim 1; Ex.1022-0100('213 Application), original claim 1. Further, claims 3 and 4 of both applications require the composition of claim 1 to be “non-enteric-coated” and “a tablet,” respectively.

Ex.2026(WO2009/139888), claims 3, 4; Ex.1022-0100('213 Application), original claims 3, 4. It is clear that the Examiner considered the ISR, which specifically identified the portions of Ionescu now cited by Petitioner, when examining the claims of the '213 application.

Thus, the Examiner considered at least five documents sharing the Ionescu disclosure at least three separate times as well as an ISR that identifies the same disclosure as the Petition, (Ex.1022-0707(IDS considered July 19, 2011); Ex.1022-1100(IDS considered February 23, 2012); Ex.1022-2027(IDS considered August

24, 2013)), and each time determined that other references—all of which were overcome during prosecution—were more relevant.

2. Atadja, Gibson, and Pharmion-PR are substantially the same as references previously presented and extensively discussed during prosecution

Atadja, Gibson, and Pharmion-PR, cited by Petitioner in Grounds 2 and 3, add nothing that is not cumulative with either Ionescu or the references cited by the Examiner during prosecution. As noted above, Petitioner uses these secondary references to support its obviousness and obvious to try theories. Pet., 31-38, 58-62. However, these disclosures are also cumulative. First, Atadja presents only boilerplate language and is cumulative over the art considered and overcome during prosecution. Atadja’s generic discussion of possible formulations for chemotherapeutic drugs had been considered and addressed by the Office in references cited in prior art rejections. Ex.1022-0644-0655(Office Action dated August 1, 2011); Ex.1022-1072-1083(Office Action dated February 28, 2012); Ex.1022-2015-2025(Office Action dated August 29, 2013); Ex.2033(Zeldis) at 21:38-23:19 (disclosing generic “Oral Dosage Forms” including “tablets (e.g., chewable tablets), caplets, capsules, and liquids (e.g., flavored syrups).”), 15:38-16:4 (disclosing “azacytidine” as one of several exemplary “[s]econd active agents....”); Ex.1019(Redkar) at ¶[0128] (disclosing various oral formulations “for

example, a tablet, capsule, suspension or liquid” as well as oral liquids “in the form of aqueous or oily solutions, suspensions, emulsions, syrups or elixirs....”), [0003] (disclosing “[a] few azacytosine nucleosides, such as...5-azacytidine....”); Ex.1021(Sands) at ¶[0040] (generically disclosing “pharmaceutical composition[s that] may be in a form of tablet or capsule.”), [0012] (disclosing “water soluble and acid-labile drugs such as cytidine analogs (e.g.,...5’-azacytidine)....”). Ultimately, each prior art rejection based on these references was overcome during prosecution.

Second, Gibson was squarely before the Examiner during prosecution because it is directly cited in the ’628 patent. Ex.1001(’628 patent), 37:24-32. Indeed, this is expressly and repeatedly acknowledged by Petitioner. Pet., 2 (“Gibson—described by the ’628 patent. . .”), 11, 33, 36, 41-42, 43. Gibson is a general formulation textbook that does not mention 5-azacytidine, much less a non-enteric coated tablet formulation of 5-azacytidine. *See* VI.C. As such, Gibson is nothing more than cumulative over the more relevant—but still deficient—references cited by the Examiner in the properly overcome prior art rejections discussed above.

Finally, Petitioner cites Pharmion-PR in Ground 3 and alleges that it “discloses a clinical study where patients with MDS were orally administered 5-

azacytidine.” Pet., 3. Petitioner describes Pharmion-PR as “report[ing], for example, that 60 and 80 mg of oral 5-azacytidine reached 18% bioavailability relative to SC” 5-azacytidine. *Id.*, 61. Pharmion-PR does not provide any information as to the formulation of 5-azacytidine used.¹¹ See VI.D; Ex.1010(Pharmion-PR). Pharmion-PR is cumulative with at least Ex.2040(Ward) or Ex.2041(WO2008/028193), which were both provided in the first IDS filed and considered by the Examiner. Ex.1022-0185-0187(IDS submitted April 2, 2010); Ex.1022-0707-0709(IDS considered July 19, 2011). Ward’s abstract, entitled “An oral dosage formulation of azacitidine: A pilot pharmacokinetic study,” like Pharmion-PR, reports that “a multicenter, single-treatment study of oral azacitidine is underway in subjects with MDS, AML, or solid tumors” to “assess[] the safety, tolerability and pharmacokinetics of escalating single doses of orally administered azacitidine,” but it also does not disclose a non-enteric coated tablet of 5-azacytidine. Ex.2040(Ward). Pharmion-PR adds nothing beyond this disclosure considered by the Examiner during prosecution. Additionally, WO2008/028193 discloses “oral dosage forms of 5-azacytidine” tablets that “were [] *enteric*

¹¹ Further, as discussed below, Petitioner’s position is fatally flawed by failing to consider the state of the art concerning 5-azacytidine.

coated....” Ex.2041(WO2008/028193), ¶[00130]. These enteric coated 5-azacytidine tablets were used in “[a] clinical study...in patients with myelodysplastic syndromes, acute myelogenous leukemia, or solid tumors.” Ex.2041(WO2008/028193), ¶[00142]. As in Pharmion-PR, the formulations of WO2008/028193 were provided as 60 mg or 80 mg doses, with the 80 mg formulation providing “[b]ioavailability relative to the historical SC 5-azacytidine [of] 18%.” Ex.2041(WO2008/028193), ¶¶[00156]-[00159]. Not only is Pharmion-PR cumulative to disclosures considered by the Examiner, but the references also indicate to a POSA as of December 2008 that the 5-azacytidine disclosed in Pharmion-PR was an enteric coated tablet as described in WO2008/028193 and ***not the claimed non-enteric coated tablet***.

In any event, the Board has held that the first prong of *Advanced Bionics* is met by a petition relying upon a primary reference that was before the Office during prosecution even if the petitioner combines the primary reference with secondary references that were not before the Office to challenge patent claims in the alternative or to challenge dependent claims. *See Samsung Electronics Co., Ltd. v. Power2B, Inc.*, No. IPR2021-01190, Paper 11 at 16-17 (P.T.A.B. Jan. 6, 2022) (non-precedential). This is clearly the case here, where Petitioner relies primarily on Ionescu, which was before the Office during examination (*see*

IX.A.1.aIX.A.1.a), and only relies on the secondary references to support their fatally flawed obviousness motivations or in the alternative.

For these reasons, Step 1 of *Advanced Bionics* is met for the secondary references.

B. Step 2 of *Advanced Bionics* Favors Denying Institution Under § 325(D) Because Petitioner Has Not Demonstrated That The Office Erred in A Manner Material to The Patentability of The Challenged Claims

1. The Examiner did not err in evaluating the prior art because the art fails to disclose non-enteric coated tablets of 5-azacytidine

Petitioner provides conclusory arguments as to why the Examiner allegedly erred. As recent Board decisions make clear, this is not sufficient. *See Ivantis, Inc., Alcon Research, LLC, Alcon Vision, LLC, and Alcon Inc., v. Sight Sciences, Inc.*, No. IPR2022-01530, Paper 14 at 18, 23 (P.T.A.B. Mar. 27, 2023) (non-precedential) (holding that where a “Petitioner has not articulated how Examiner erred during the prosecution” it weighs in the patent owner’s favor). Put simply, Petitioner’s position is that, because Petitioner argues the claims are anticipated or obvious over Ionescu, the Examiner must have erred during prosecution because the claims were not rejected over Ionescu. Pet., 63-64. However, Petitioner is incorrect in alleging that the Examiner erred in his treatment of a “sugar coating” disclosed by Ionescu. Pet., 63-64. As discussed at length (*see* VII.A.1.a) and

incorporated by reference herein, despite Petitioner's assertions otherwise,

nowhere does Ionescu disclose a non-enteric coated tablet or that a formulation of 5-azacytidine with a sugar coating would be a non-enteric coated tablet.

Additionally, a POSA would have understood that Ionescu's disclosure that tablets "may be coated with a concentrated solution of sugar" is not synonymous with a non-enteric coated tablet. *See* VII.A. The Petition further fails to address recent decisions holding that the mere disagreement on the interpretation of a reference where reasonable minds could disagree is not sufficient to establish error.

Advanced Bionics, Paper 6 at 9; *see also Intel Corporation v. ACQIS LLC*, No.

IPR2021-01105, Paper 15 (P.T.A.B. Dec. 12, 2022) (non-precedential). Given the

evidence in Petitioner's own exhibits, the additional references cited herein, and

Dr. Berkland's testimony, Petitioner has failed to show error in the Examiner's

understanding of Ionescu. *See* Ex.2001(Berkland Decl.) at ¶¶48-85. Moreover,

Petitioner has failed to demonstrate that the Examiner did not sufficiently evaluate

Ionescu. "Petitioner bears the burden to 'demonstrate[] that the Office erred in a

manner material to the patentability of challenged claims,'" and the Board has

recently held that merely "equat[ing] the examiner's silence in discussing relevant

prior art to a material error" is not persuasive. *Ivantis, Inc., Alcon Research, LLC.,*

Alcon Vision, LLC, and Alcon Inc. v. Sight Sciences, Inc., No. IPR2022-01540,

Paper 14 (P.T.A.B. Mar. 22, 2023) (non-precedential), 14 (quoting *Advanced Bionics*, Paper 6 at 8). The file history and the Examiner’s statements make clear that the Examiner considered Ionescu and an ISR citing nearly all of the portions of Ionescu Petitioner relies upon in the Petition during prosecution as discussed above. *See* IX.A.1.c.

Thus, Petitioner has not established how the Examiner allegedly erred in his evaluation of the asserted references including Ionescu—which does not disclose nor would be understood by a POSA to suggest a non-enteric coated tablet of 5-azacytidine.

2. The Examiner considered Ionescu, making Petitioner’s citation to *Lyft* clearly distinguishable on the facts

Relying on *Lyft*, Petitioner asserts that there is “no evidence that the Examiner substantively considered Ionescu” because “[t]he only mention of Ionescu is by way of an IDS, and the Examiner never applied Ionescu to reject any claims.” Pet., 63. Petitioner is incorrect and mischaracterizes the prosecution record.

First, earlier this year, the PTAB found the citation of a reference on an IDS sufficient to establish that the Examiner considered the document provided. *See Risen (Suzhou) Pharma Tech Co., Ltd. V. Alzheon, Inc.*, No. PGR2022-00051, Paper 14 at 47-48 (P.T.A.B. Jan. 13, 2023) (non-precedential) (“references

considered in an IDS are considered presented to the Office, it is clear that [the challenging reference] was previously presented to the Office.”) (citing *Advanced Bionics*, Paper 6 at 7). Indeed, the Board has recently reiterated that “there is no requirement that the Examiner needs to rely on a reference in a rejection during prosecution in order for the reference to be ‘considered’ during prosecution.” *Ivantis, Inc., Alcon Research, LLC, Alcon Vision, LLC, and Alcon Inc., v. Sight Sciences, Inc.*, No. IPR2022-01530, Paper 14 at 17, 22-23 (P.T.A.B. Mar. 27, 2023) (non-precedential) (citing *Advanced Bionics*, Paper 6 at 7-8).

Second, the Examiner of the ’213 application explicitly noted his consideration on the IDSs, in the Office actions, and in the Notice of Allowance. *See* Ex.1022-0707-0709(IDS considered July 19, 2011); Ex.1022-1100-1104(IDS considered February 23, 2012); Ex.1022-2027(IDS considered August 24, 2013); Ex.1022-0646(Office Action dated August 2, 2011); Ex.1022-1074(Office Action dated February 28, 2012); Ex.1022-2017(Office Action dated August 29, 2013); Ex.1022-2138-2139(Notice of Allowance). As discussed above (*see* IX.A.1.a, IX.A.1.b), Applicant submitted at least five documents sharing the Ionescu disclosure at least three different times, and the Examiner considered them each time. Ex.1022-0185-0187(IDS submitted April 2, 2010); Ex.1022-0707-0709(IDS considered July 19, 2011); Ex.1022-0735(IDS submitted December 1, 2011);

Ex.1022-1100-1104(IDS considered February 23, 2012); Ex.1022-1129(IDS submitted September 5, 2012); Ex.1022-2027(IDS considered August 24, 2013).

Third, *Lyft* is distinguishable because the petitioner in *Lyft* relied on a combination of references that was not before the Examiner. The *Lyft* Board exclusively considered Grounds involving cited art in combination with another uncited and non-cumulative reference. *Lyft v. Rideshare Displays Inc.*, No. IPR2021-01601, Paper 7 at 16-17 (P.T.A.B. Apr. 11, 2022). Here, Ground 1 only involves a single reference—Ionescu—that the Examiner considered multiple times. *See* IX.A.1.a, IX.A.1.b. Further, Grounds 2 or 3 rely primarily on the considered Ionescu reference, and the secondary references are at most cumulative to references considered and cited by the Examiner in prior art rejections that were properly overcome during prosecution. *See* IX.A.2.

3. The experts' declarations and modeling do not provide new evidence that warrant reconsideration of the prior art or arguments

Petitioner argues that its experts' declarations and modeling are additional evidence and facts presented in the Petition that warrant reconsideration of the prior art or arguments. Pet., 64. Petitioner is incorrect.

a. Dr. Buckton's declaration does not present additional evidence that warrants reconsideration of the prior art

As an initial matter, while Dr. Buckton's declaration contains 193 paragraphs, most of them are not cited or relied upon in the Petition to challenge the independent claims. *See* Pet., 20-23 (Ground 1 challenges to claims 1 and 28 without a citation to Dr. Buckton's declaration); 31-38 (Ground 2 challenges to claims 1 and 28 citing only seven paragraphs of Dr. Buckton's declaration); 58-62 (Ground 3 citing only four paragraphs of Dr. Buckton's declaration).

Further, the mere assertion that a declaration provides new information without more is not sufficient to establish error. *See Nespresso USA, Inc. v. K-Fee System GMHB*, No. IPR2021-01222, Paper 9 at 26 (P.T.A.B. Jan. 6, 2022) (non-precedential) (denying institution on 325(d), finding the mere assertion that petitioner's invalidity challenge "is supported by expert testimony, which the Examiner did not have" "is ineffective to show that the Examiner materially erred by failing to discuss the same prior art combinations advanced in the Petition"). In this case, the Petition cites portions of Dr. Buckton's declaration that contain unsupported, conclusory statements. *See, e.g.,* Ex.1002(Buckton Decl.), ¶¶44, 126 (cited in Pet., 37), 128 (cited in Pet., 37), 140 (cited in Pet., 41), 167 (cited in Pet., 52), and 187 (cited in Pet., 60). The Board stated in *Xerox* that such "conclusory and unsupported" declaration testimony "adds little to the conclusory assertion[s]

for which it is offered to support, and is entitled to little weight.” *Xerox Corp. v. Bytemark, Inc.*, No. IPR2022-00624, Paper 9 at 15 (P.T.A.B. Aug. 24, 2022) (precedential).

And even when Dr. Buckton cites evidence such as Remington as support for his argument regarding sugar coating techniques, he ignores the disclosure of ***sugar-coated, enteric coated tablets present on the same page.*** See Ex.1002(Buckton Decl.), ¶141; *see also* Ex.1030-0047(Remington). Dr. Buckton does not, and cannot, establish that the references cited in the Grounds are not cumulative to teachings already considered by the Examiner and overcome during prosecution. The Board recently confirmed that where a petitioner’s expert “look[s] at substantially the same references as the Examiner and comes to a different conclusion,... [it] is not compelling, especially when there is no explanation how the Examiner erred.” *Ivantis, Inc., Alcon Research, LLC, Alcon Vision, LLC, and Alcon Inc., v. Sight Sciences, Inc.*, No. IPR2022-01530, Paper 14 at 18, 23, 29 (P.T.A.B. Mar. 27, 2023) (non-precedential). Thus, Dr. Buckton’s declaration does not provide any new information that merits further consideration of the prior art references.

b. Dr. Batchelor's declaration does not present additional evidence that warrants reconsideration of the prior art references

Dr. Batchelor's declaration and the *in silico* modeling presented therein is only cited for nine dependent claims and does not establish error. Pet., 29-31, 50-51. Petitioner's limited citations to Dr. Batchelor's declaration in the Petition do not include any citations concerning independent claims 1 or 28 (Pet., 13-15, 29-31, 50-51), and so the declaration provides no new information regarding those claims beyond what was overcome during prosecution. Even Petitioner acknowledges that the modeling is "not necessary" to Ground 1 or Ground 2. Pet., 29, 50. The Petition is also entirely silent as to the modeling in Ground 3. *Id.*, 58-62. Further, Petitioner has not identified an error committed by the Office by not

considering the modeling.¹² This is at least because the modeling's alleged applicability is limited to pharmacokinetic properties, which are recited only in a subset of nine dependent claims and not recited in either of the independent claims. Ex.1001('628 patent), Claims 1, 11, 18, 20-22, 28, 38, 40, 42-43.

Moreover, Petitioner cannot demonstrate the modeling invalidates even these dependent claims at least because Petitioner cannot demonstrate the independent claims of the '628 patent are invalid as discussed above. *See* VII-VIII. Nowhere does Dr. Batchelor or Petitioner assert that the *in silico* modeling discloses a non-enteric coated tablet of 5-azacytidine. *See* Ex.1003(Batchelor

¹² Patent Owner notes that there are several errors in Dr. Batchelor's analysis. For example, Dr. Batchelor used a hydrolysis rate constant reported for a less acidic environment (pH values between 4.5 and 8.0) than that present in the modeled highly acidic stomach (pH 1.1). Ex.1003(Batchelor Decl.), ¶¶34-36, 41, 42, 46; Ex.2043(Lieberman Vol. 2), 349-50; Ex.2015(Evans), 1035; Ex.2001(Berkland Decl.) at ¶71. However, Dr. Batchelor does not explain why the hydrolysis rate in a far less acidic setting would predict hydrolysis in the stomach. Patent Owner does not address Dr. Batchelor's declaration fully here because it is not relevant to the independent claims and does not establish error.

Decl.); Pet., 13-15, 29-31, 50-51. Because Petitioner has failed to establish that any of the cited references disclose the independent claims' limitation of "a non-enteric coated tablet" of 5-azacytidine, the *in silico* modeling cannot establish obviousness of any dependent claims.

Additionally, Petitioner's reliance on *Wabco Holdings v. Transtex Composite* is misplaced. As Petitioner itself notes, institution in *Wabco* "relied on 'purported results of **actual testing**[...]'". Pet., 64 (quoting *Wabco Holdings Inc., et al., v. Transtex Composite Inc.*, No. IPR2018-00737, Paper 8 at 8-11 (P.T.A.B. Sep. 27, 2018) (non-precedential)). However, *Wabco* is distinguishable at least because Petitioner does not rely on **actual testing** here but merely modeling.

Furthermore, Dr. Batchelor's declaration should be discounted because it does not consider enzymatic metabolism of 5-azacytidine by cytidine deaminase. Therefore, Dr. Batchelor's declaration also does not provide any new information that merits further consideration.

For these reasons alone, Dr. Batchelor's self-admitted "not necessary" modeling does not provide any new information that merits further consideration by the Board.

X. CONCLUSION

For the above reasons, Patent Owner respectfully requests that the Board deny Petitioner's Petition for *inter partes* review of the '628 Patent in its entirety.

Respectfully submitted,

Date: May 15, 2023

By: /Heather M. Petruzzi/
Heather Petruzzi (Reg. No. 71,270)

CERTIFICATION UNDER 37 C.F.R. §42.24(d)

I hereby certify that the foregoing, Patent Owner's Preliminary Response, contains 12,797 words as measured by the word processing software used to prepare the document, in compliance with 37 C.F.R. § 42.24(d), excluding the parts of the exempted from the word count by 37 C.F.R. § 42.24(a)(1).

By: /Heather M. Petruzzi/
Heather Petruzzi (Reg. No. 71,270)

CERTIFICATE OF SERVICE

I hereby certify that on May 15, 2023, I caused a true and correct copies of the following materials:

- Patent Owner's Preliminary Response
- Patent Owner's Exhibit List
- Exhibits 2001-2004, 2006-2045, and 2047
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